

# Ciliary signalling in cancer

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## Abstract

© 2018, Macmillan Publishers Ltd., part of Springer Nature. Although tumours initiate from oncogenic changes in a cancer cell, subsequent tumour progression and therapeutic response depend on interactions between the cancer cells and the tumour microenvironment (TME). The primary monocilium, or cilium, provides a spatially localized platform for signalling by Hedgehog, Notch, WNT and some receptor tyrosine kinase pathways and mechanosensation. Changes in ciliation of cancer cells and/or cells of the TME during tumour development enforce asymmetric intercellular signalling in the TME. Growing evidence indicates that some oncogenic signalling pathways as well as some targeted anticancer therapies induce ciliation, while others repress it. The links between the genomic profile of cancer cells, drug treatment and ciliary signalling in the TME likely affect tumour growth and therapeutic response.

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## References

- [1] Reiter, J. F. & Leroux, M. R. Genes and molecular pathways underpinning ciliopathies. *Nat. Rev. Mol. Cell Biol.* 18, 533–547 (2017).
- [2] Rosenbaum, J. L. & Witman, G. B. Intraflagellar transport. *Nat. Rev. Mol. Cell Biol.* 3, 813–825 (2002).
- [3] Pazour, G. J. & Rosenbaum, J. L. Intraflagellar transport and cilia-dependent diseases. *Trends Cell Biol.* 12, 551–555 (2002).
- [4] Quarumby, L. M. Cellular deflagellation. *Int. Rev. Cytol.* 233, 47–91 (2004).
- [5] Wang, Q., Pan, J. & Snell, W. J. Intraflagellar transport particles participate directly in cilium-generated signaling in *Chlamydomonas*. *Cell* 125, 549–562 (2006).
- [6] Pan, J., Misamore, M. J., Wang, Q. & Snell, W. J. Protein transport and signal transduction during fertilization in *chlamydomonas*. *Traffic* 4, 452–459 (2003).
- [7] Dutcher, S. K. The awesome power of dikaryons for studying flagella and basal bodies in *Chlamydomonas reinhardtii*. *Cytoskeleton* 71, 79–94 (2014).
- [8] Awata, J. et al. NPHP4 controls ciliary trafficking of membrane proteins and large soluble proteins at the transition zone. *J. Cell Sci.* 127, 4714–4727 (2014).
- [9] Quarumby, L. M. & Parker, J. D. Cilia and the cell cycle? *J. Cell Biol.* 169, 707–710 (2005).
- [10] Pan, J., Seeger-Nukpezah, T. & Golemis, E. A. The role of the cilium in normal and abnormal cell cycles: emphasis on renal cystic pathologies. *Cell. Mol. Life Sci.* 70, 1849–1874 (2013).
- [11] Korobeynikov, V., Deneka, A. Y. & Golemis, E. A. Mechanisms for nonmitotic activation of Aurora-A at cilia. *Biochem. Soc. Trans.* 45, 37–49 (2017).
- [12] Ishikawa, H. & Marshall, W. F. Ciliogenesis: building the cell's antenna. *Nat. Rev. Mol. Cell Biol.* 12, 222–234 (2011).
- [13] Goto, H., Inaba, H. & Inagaki, M. Mechanisms of ciliogenesis suppression in dividing cells. *Cell. Mol. Life Sci.* 74, 881–890 (2017).
- [14] Sung, C. H. & Leroux, M. R. The roles of evolutionarily conserved functional modules in cilia-related trafficking. *Nat. Cell Biol.* 15, 1387–1397 (2013).

- [15] Phua, S. C. et al. Dynamic remodeling of membrane composition drives cell cycle through primary cilia excision. *Cell* 168, 264–279.e15 (2017).
- [16] Sanchez, I. & Dynlacht, B. D. Cilium assembly and disassembly. *Nat. Cell Biol.* 18, 711–717 (2016).
- [17] Keeling, J., Tsiokas, L. & Maskey, D. Cellular mechanisms of ciliary length control. *Cells* 5, 6 (2016).
- [18] Nikonova, A. S., Astsaturov, I., Serebriiskii, I. G., Dunbrack, R. L. Jr & Golemis, E. A. Aurora A kinase (AURKA) in normal and pathological cell division. *Cell. Mol. Life Sci.* 70, 661–687 (2013).
- [19] Cholewa, B. D., Liu, X. & Ahmad, N. The role of polo-like kinase 1 in carcinogenesis: cause or consequence? *Cancer Res.* 73, 6848–6855 (2013).
- [20] Benzing, T. & Walz, G. Cilium-generated signaling: a cellular GPS? *Curr. Opin. Nephrol. Hypertens.* 15, 245–249 (2006).
- [21] Singla, V. & Reiter, J. F. The primary cilium as the cell's antenna: signaling at a sensory organelle. *Science* 313, 629–633 (2006).
- [22] Bangs, F. & Anderson, K. V. Primary cilia and mammalian Hedgehog signaling. *Cold Spring Harbor Persp. Biol.* 9, a028175 (2017).
- [23] Rohatgi, R., Milenkovic, L. & Scott, M. P. Patched1 regulates hedgehog signaling at the primary cilium. *Science* 317, 372–376 (2007).
- [24] Corbit, K. C. et al. Vertebrate Smoothed functions at the primary cilium. *Nature* 437, 1018–1021 (2005).
- [25] Li, J. L. et al. DLL4-Notch signaling mediates tumor resistance to anti-VEGF therapy in vivo. *Cancer Res.* 71, 6073–6083 (2011).
- [26] Korkaya, H. & Wicha, M. S. HER-2, notch, and breast cancer stem cells: targeting an axis of evil. *Clin. Cancer Res.* 15, 1845–1847 (2009).
- [27] Ezratty, E. J. et al. A role for the primary cilium in Notch signaling and epidermal differentiation during skin development. *Cell* 145, 1129–1141 (2011).
- [28] Stasiulewicz, M. et al. A conserved role for Notch signaling in priming the cellular response to Shh through ciliary localisation of the key Shh transducer Smo. *Development* 142, 2291–2303 (2015).
- [29] Kong, J. H. et al. Notch activity modulates the responsiveness of neural progenitors to sonic hedgehog signaling. *Dev. Cell* 33, 373–387 (2015).
- [30] Wallingford, J. B. & Mitchell, B. Strange as it may seem: the many links between Wnt signaling, planar cell polarity, and cilia. *Genes Dev.* 25, 201–213 (2011).
- [31] Hankey, W., Frankel, W. L. & Groden, J. Functions of the APC tumor suppressor protein dependent and independent of canonical WNT signaling: implications for therapeutic targeting. *Cancer Metastasis Rev.* 37, 159–172 (2018).
- [32] Corbit, K. C. et al. Kif3a constrains beta-catenin-dependent Wnt signalling through dual ciliary and non-ciliary mechanisms. *Nat. Cell Biol.* 10, 70–76 (2008).
- [33] Simons, M. et al. Inversin, the gene product mutated in nephronophthisis type II, functions as a molecular switch between Wnt signaling pathways. *Nat. Genet.* 37, 537–543 (2005).
- [34] Ocbina, P. J., Tuson, M. & Anderson, K. V. Primary cilia are not required for normal canonical Wnt signaling in the mouse embryo. *PLoS ONE* 4, e6839 (2009).
- [35] Ross, A. J. et al. Disruption of Bardet-Biedl syndrome ciliary proteins perturbs planar cell polarity in vertebrates. *Nat. Genet.* 37, 1135–1140 (2005).
- [36] Gerdes, J. M. et al. Disruption of the basal body compromises proteasomal function and perturbs intracellular Wnt response. *Nat. Genet.* 39, 1350–1360 (2007).
- [37] Schneider, L. et al. PDGFR $\alpha$  signaling is regulated through the primary cilium in fibroblasts. *Curr. Biol.* 15, 1861–1866 (2005).
- [38] Schneider, L. et al. Directional cell migration and chemotaxis in wound healing response to PDGF-AA are coordinated by the primary cilium in fibroblasts. *Cell Physiol. Biochem.* 25, 279–292 (2010).
- [39] Schneider, L. et al. The NaH exchanger NHE1 is required for directional migration stimulated via PDGFR- $\alpha$  in the primary cilium. *J. Cell Biol.* 185, 163–176 (2009).
- [40] Umberger, N. L. & Caspary, T. Ciliary transport regulates PDGF-AA/ $\alpha$  signaling via elevated mammalian target of rapamycin signaling and diminished PP2A activity. *Mol. Biol. Cell* 26, 350–358 (2015).
- [41] Boehlke, C. et al. Primary cilia regulate mTORC1 activity and cell size through Lkb1. *Nat. Cell Biol.* 12, 1115–1122 (2010).
- [42] Christensen, S. T., Morthorst, S. K., Mogensen, J. B. & Pedersen, L. B. Primary cilia and coordination of receptor tyrosine kinase (RTK) and transforming growth factor beta (TGF- $\beta$ ) signaling. *Cold Spring Harbor Persp. Biol.* 9, a028167 (2017).
- [43] Zhu, D., Shi, S., Wang, H. & Liao, K. Growth arrest induces primary-cilium formation and sensitizes IGF--receptor signaling during differentiation induction of 3T3-L1 preadipocytes. *J. Cell Sci.* 122, 2760–2768 (2009).

- [44] Clement, C. A. et al. TGF-beta signaling is associated with endocytosis at the pocket region of the primary cilium. *Cell Rep.* 3, 1806-1814 (2013).
- [45] Seeger-Nukpezah, T. & Golemis, E. A. The extracellular matrix and ciliary signaling. *Curr. Opin. Cell Biol.* 24, 652-661 (2012).
- [46] McMurray, R. J., Wann, A. K., Thompson, C. L., Connelly, J. T. & Knight, M. M. Surface topography regulates wnt signaling through control of primary cilia structure in mesenchymal stem cells. *Sci. Rep.* 3, 3545 (2013).
- [47] Wann, A. K. et al. Primary cilia mediate mechanotransduction through control of ATP-induced Ca signaling in compressed chondrocytes. *FASEB J.* 26, 1663-1671 (2012).
- [48] Chen, J. C., Hoey, D. A., Chua, M., Bellon, R. & Jacobs, C. R. Mechanical signals promote osteogenic fate through a primary cilia-mediated mechanism. *FASEB J.* 30, 1504-1511 (2016).
- [49] Hilgendorf, K. I., Johnson, C. T. & Jackson, P. K. The primary cilium as a cellular receiver: organizing ciliary GPCR signaling. *Curr. Opin. Cell Biol.* 39, 84-92 (2016).
- [50] Hopkins, B. D., Goncalves, M. D. & Cantley, L. C. Obesity and cancer mechanisms: cancer metabolism. *J. Clin. Oncol.* 34, 4277-4283 (2016).
- [51] Iyengar, N. M., Gucalp, A., Dannenberg, A. J. & Hudis, C. A. Obesity and cancer mechanisms: tumor microenvironment and inflammation. *J. Clin. Oncol.* 34, 4270-4276 (2016).
- [52] Bangs, F. K., Schrode, N., Hadjantonakis, A. K. & Anderson, K. V. Lineage specificity of primary cilia in the mouse embryo. *Nat. Cell Biol.* 17, 113-122 (2015).
- [53] Dieckmann, N. M., Frazer, G. L., Asano, Y., Stinchcombe, J. C. & Griffiths, G. M. The cytotoxic T lymphocyte immune synapse at a glance. *J. Cell Sci.* 129, 2881-2886 (2016).
- [54] Finetti, F., Paccani, S. R., Rosenbaum, J. & Baldari, C. T. Intraflagellar transport: a new player at the immune synapse. *Trends Immunol.* 32, 139-145 (2011).
- [55] McDermott, K. M., Liu, B. Y., Tlsty, T. D. & Pazour, G. J. Primary cilia regulate branching morphogenesis during mammary gland development. *Curr. Biol.* 20, 731-737 (2010).
- [56] Garcia-Zaragoza, E. et al. Intraepithelial paracrine Hedgehog signaling induces the expansion of ciliated cells that express diverse progenitor cell markers in the basal epithelium of the mouse mammary gland. *Dev. Biol.* 372, 28-44 (2012).
- [57] Yuan, K. et al. Primary cilia are decreased in breast cancer: analysis of a collection of human breast cancer cell lines and tissues. *J. Histochem. Cytochem.* 58, 857-870 (2010).
- [58] Menzl, I. et al. Loss of primary cilia occurs early in breast cancer development. *Cilia* 3, 7 (2014).
- [59] Hassounah, N. B. et al. Inhibition of ciliogenesis promotes Hedgehog signaling, tumorigenesis, and metastasis in breast cancer. *Mol. Cancer Res.* 15, 1421-1430 (2017).
- [60] Seeley, E. S., Carriere, C., Goetze, T., Longnecker, D. S. & Korc, M. Pancreatic cancer and precursor pancreatic intraepithelial neoplasia lesions are devoid of primary cilia. *Cancer Res.* 69, 422-430 (2009).
- [61] Schimmack, S. et al. Epithelial to stromal re-distribution of primary cilia during pancreatic carcinogenesis. *PLoS ONE* 11, e0164231 (2016).
- [62] Emoto, K. et al. Presence of primary cilia in cancer cells correlates with prognosis of pancreatic ductal adenocarcinoma. *Hum. Pathol.* 45, 817-825 (2014).
- [63] Cano, D. A., Murcia, N. S., Pazour, G. J. & Hebrok, M. Orpk mouse model of polycystic kidney disease reveals essential role of primary cilia in pancreatic tissue organization. *Development* 131, 3457-3467 (2004).
- [64] Cano, D. A., Sekine, S. & Hebrok, M. Primary cilia deletion in pancreatic epithelial cells results in cyst formation and pancreatitis. *Gastroenterology* 131, 1856-1869 (2006).
- [65] Hassounah, N. B. et al. Primary cilia are lost in preinvasive and invasive prostate cancer. *PLoS ONE* 8, e68521 (2013).
- [66] Egeberg, D. L. et al. Primary cilia and aberrant cell signaling in epithelial ovarian cancer. *Cilia* 1, 15 (2012).
- [67] Ho, L. et al. Primary cilia attenuate hedgehog signalling in neoplastic chondrocytes. *Oncogene* 32, 5388-5396 (2013).
- [68] Plotnikova, O. V., Golemis, E. A. & Pugacheva, E. N. Cell cycle-dependent ciliogenesis and cancer. *Cancer Res.* 68, 2058-2061 (2008).
- [69] Han, Y. G. et al. Dual and opposing roles of primary cilia in medulloblastoma development. *Nat. Med.* 15, 1062-1065 (2009).
- [70] Wong, S. Y. et al. Primary cilia can both mediate and suppress Hedgehog pathway-dependent tumorigenesis. *Nat. Med.* 15, 1055-1061 (2009).
- [71] Niewiadomski, P. et al. Gli protein activity is controlled by multisite phosphorylation in vertebrate Hedgehog signaling. *Cell Rep.* 6, 168-181 (2014).
- [72] Berman, D. M. et al. Widespread requirement for Hedgehog ligand stimulation in growth of digestive tract tumours. *Nature* 425, 846-851 (2003).

- [73] Thayer, S. P. et al. Hedgehog is an early and late mediator of pancreatic cancer tumorigenesis. *Nature* 425, 851–856 (2003).
- [74] Bailey, J. M. et al. Sonic hedgehog promotes desmoplasia in pancreatic cancer. *Clin. Cancer Res.* 14, 5995–6004 (2008).
- [75] Tape, C. J. et al. Oncogenic KRAS regulates tumor cell signaling via stromal reciprocity. *Cell* 165, 910–920 (2016).
- [76] O'Toole, S. A. et al. Hedgehog overexpression is associated with stromal interactions and predicts for poor outcome in breast cancer. *Cancer Res.* 71, 4002–4014 (2011).
- [77] Shaw, A., Gipp, J. & Bushman, W. The Sonic Hedgehog pathway stimulates prostate tumor growth by paracrine signaling and recapitulates embryonic gene expression in tumor myofibroblasts. *Oncogene* 28, 4480–4490 (2009).
- [78] Buller, N. V. et al. Stromal Indian hedgehog signaling is required for intestinal adenoma formation in mice. *Gastroenterology* 148, 170–180.e6 (2015).
- [79] Pan, J., Wang, Q. & Snell, W. J. An aurora kinase is essential for flagellar disassembly in *Chlamydomonas*. *Dev. Cell* 6, 445–451 (2004).
- [80] Pugacheva, E. N., Jablonski, S. A., Hartman, T. R., Henske, E. P. & Golemis, E. A. HEF1-dependent Aurora A activation induces disassembly of the primary cilium. *Cell* 129, 1351–1363 (2007).
- [81] Nikonova, A. S. et al. Nedd9 restrains renal cystogenesis in Pkd1 mice. *Proc. Natl Acad. Sci. USA* 111, 12859–12864 (2014).
- [82] Nikonova, A. S., Gaponova, A. V., Kudinov, A. E. & Golemis, E. A. CAS proteins in health and disease: an update. *IUBMB Life* 66, 387–395 (2014).
- [83] Xu, J. et al. VHL Inactivation Induces HEF1 and Aurora kinase A. *J. Am. Soc. Nephrol.* 21, 2041–2046 (2010).
- [84] Dere, R., Perkins, A. L., Bawa-Khalife, T., Jonasch, D. & Walker, C. L.  $\beta$ -catenin links von Hippel-Lindau to aurora kinase A and loss of primary cilia in renal cell carcinoma. *J. Am. Soc. Nephrol.* 26, 553–564 (2015).
- [85] Kobayashi, T. et al. HDAC2 promotes loss of primary cilia in pancreatic ductal adenocarcinoma. *EMBO Rep.* 18, 334–343 (2017).
- [86] Tucker, R. W., Scher, C. D. & Stiles, C. D. Centriole deciliation associated with the early response of 3T3 cells to growth factors but not to SV40. *Cell* 18, 1065–1072 (1979).
- [87] Jacoby, M. et al. INPP5E mutations cause primary cilium signaling defects, ciliary instability and ciliopathies in human and mouse. *Nat. Genet.* 41, 1027–1031 (2009).
- [88] Kasahara, K. et al. EGF receptor kinase suppresses ciliogenesis through activation of USP8 deubiquitinase. *Nat. Commun.* 9, 758 (2018).
- [89] Nielsen, B. S. et al. PDGFR $\beta$  and oncogenic mutant PDGFR $\alpha$  D842V promote disassembly of primary cilia through a PLC $\gamma$ - and AURKA-dependent mechanism. *J. Cell Sci.* 128, 3543–3549 (2015).
- [90] Morrissy, A. S. et al. Divergent clonal selection dominates medulloblastoma at recurrence. *Nature* 529, 351–357 (2016).
- [91] Jones, D. T. et al. Dissecting the genomic complexity underlying medulloblastoma. *Nature* 488, 100–105 (2012).
- [92] Bonilla, X. et al. Genomic analysis identifies new drivers and progression pathways in skin basal cell carcinoma. *Nat. Genet.* 48, 398–406 (2016).
- [93] Cao, M. & Zhong, Q. Cilia in autophagy and cancer. *Cilia* 5, 4 (2015).
- [94] Wang, S., Livingston, M. J., Su, Y. & Dong, Z. Reciprocal regulation of cilia and autophagy via the MTOR and proteasome pathways. *Autophagy* 11, 607–616 (2015).
- [95] Tang, Z. et al. Autophagy promotes primary ciliogenesis by removing OFD1 from centriolar satellites. *Nature* 502, 254–257 (2013).
- [96] Pampliega, O. et al. Functional interaction between autophagy and ciliogenesis. *Nature* 502, 194–200 (2013).
- [97] Gerhardt, C., Leu, T., Lier, J. M. & Ruther, U. The cilia-regulated proteasome and its role in the development of ciliopathies and cancer. *Cilia* 5, 14 (2016).
- [98] Liu, Y. P. et al. Ciliopathy proteins regulate paracrine signaling by modulating proteasomal degradation of mediators. *J. Clin. Invest.* 124, 2059–2070 (2014).
- [99] Kasahara, K. et al. Ubiquitin-proteasome system controls ciliogenesis at the initial step of axoneme extension. *Nat. Commun.* 5, 5081 (2014).
- [100] Legare, S., Chabot, C. & Basik, M. SPEN, a new player in primary cilia formation and cell migration in breast cancer. *Breast Cancer Res.* 19, 104 (2017).
- [101] Kim, S., Lee, K., Choi, J. H., Ringstad, N. & Dynlacht, B. D. Nek2 activation of Kif24 ensures cilium disassembly during the cell cycle. *Nat. Commun.* 6, 8087 (2015).
- [102] Rocha, C. et al. Tubulin glycosylases are required for primary cilia, control of cell proliferation and tumor development in colon. *EMBO J.* 33, 2247–2260 (2014).

- [103] Conduit, S. E. et al. A compartmentalized phosphoinositide signaling axis at cilia is regulated by INPP5E to maintain cilia and promote Sonic Hedgehog medulloblastoma. *Oncogene* 36, 5969–5984 (2017).
- [104] Yang, N. et al. INTU is essential for oncogenic Hh signaling through regulating primary cilia formation in basal cell carcinoma. *Oncogene* 36, 4997–5005 (2017).
- [105] Willemarck, N. et al. Aberrant activation of fatty acid synthesis suppresses primary cilium formation and distorts tissue development. *Cancer Res.* 70, 9453–9462 (2010).
- [106] Overgaard, C. E. et al. Deciliation is associated with dramatic remodeling of epithelial cell junctions and surface domains. *Mol. Biol. Cell* 20, 102–113 (2009).
- [107] Toriyama, M. et al. The ciliopathy-associated CPLANE proteins direct basal body recruitment of intraflagellar transport machinery. *Nat. Genet.* 48, 648–656 (2016).
- [108] Johnson, C. A. & Collis, S. J. Ciliogenesis and the DNA damage response: a stressful relationship. *Cilia* 5, 19 (2016).
- [109] Slaats, G. G. et al. Nephronophthisis-associated CEP164 regulates cell cycle progression, apoptosis and epithelial-to-mesenchymal transition. *PLoS Genet.* 10, e1004594 (2014).
- [110] Choi, H. J. et al. NEK8 links the ATR-regulated replication stress response and S phase CDK activity to renal ciliopathies. *Mol. Cell* 51, 423–439 (2013).
- [111] Litchfield, K. et al. Rare disruptive mutations in ciliary function genes contribute to testicular cancer susceptibility. *Nat. Commun.* 7, 13840 (2016).
- [112] Walentek, P. Ciliary transcription factors in cancer — how understanding ciliogenesis can promote the detection and prognosis of cancer types. *J. Pathol.* 239, 6–9 (2016).
- [113] Harlander, S. et al. Combined mutation in Vhl, Trp53 and Rb1 causes clear cell renal cell carcinoma in mice. *Nat. Med.* 23, 869–877 (2017).
- [114] Rannestad, J. The regeneration of cilia in partially deciliated Tetrahymena. *J. Cell Biol.* 63, 1009–1017 (1974).
- [115] Propst, S., Banerjee, S., Kelleher, J. K. & Margulis, L. Inhibition of cilia regeneration by antineoplastic agents: delay of band migration by vinblastine (NSC-49842), griseofulvin (NSC-34533), and -peltatin (NSC-24819). *Cancer Chemother. Rep.* 56, 557–558 (1972).
- [116] Stubblefield, E. & Brinkley, B. R. Cilia formation in Chinese hamster fibroblasts in vitro as a response to colcemid treatment. *J. Cell Biol.* 30, 645–652 (1966).
- [117] Boisvieux-Ulrich, E., Laine, M. C. & Sandoz, D. In vitro effects of taxol on ciliogenesis in quail oviduct. *J. Cell Sci.* 92, 9–20 (1989).
- [118] Sharma, N., Kosan, Z. A., Stallworth, J. E., Berbari, N. F. & Yoder, B. K. Soluble levels of cytosolic tubulin regulate ciliary length control. *Mol. Biol. Cell* 22, 806–816 (2011).
- [119] Liewer, S. & Huddleston, A. Alisertib: a review of pharmacokinetics, efficacy and toxicity in patients with hematologic malignancies and solid tumors. *Expert Opin. Investig. Drugs* 27, 105–112 (2018).
- [120] Seeger-Nukpezah, T. et al. The centrosomal kinase Plk1 localizes to the transition zone of primary cilia and induces phosphorylation of nephrocystin-1. *PLoS ONE* 7, e38838 (2012).
- [121] Lee, K. H. et al. Identification of a novel Wnt5a-CK1 $\alpha$ -varepsilon-Dvl2-Plk1-mediated primary cilia disassembly pathway. *EMBO J.* 31, 3104–3117 (2012).
- [122] Talati, C., Griffiths, E. A., Wetzler, M. & Wang, E. S. Polo-like kinase inhibitors in hematologic malignancies. *Crit. Rev. Oncol. Hematol.* 98, 200–210 (2016).
- [123] Plotnikova, O. V. et al. INPP5E interacts with AURKA, linking phosphoinositide signaling to primary cilium stability. *J. Cell Sci.* 128, 364–372 (2015).
- [124] Khan, N. A. et al. Identification of drugs that restore primary cilium expression in cancer cells. *Oncotarget* 7, 9975–9992 (2016).
- [125] Miyata, Y., Nakamoto, H. & Neckers, L. The therapeutic target Hsp90 and cancer hallmarks. *Curr. Pharm. Des.* 19, 347–365 (2013).
- [126] Nikonova, A. S. et al. Ganetespib limits ciliation and cystogenesis in autosomal-dominant polycystic kidney disease (ADPKD). *FASEB J.* 10.1096/fj.201700909R (2018).
- [127] Koene, R. J., Prizment, A. E., Blaes, A. & Konety, S. H. Shared risk factors in cardiovascular disease and cancer. *Circulation* 133, 1104–1114 (2016).
- [128] Krebber, A. M. et al. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. *Psychooncology* 23, 121–130 (2014).
- [129] Eng, J. W. et al. A nervous tumor microenvironment: the impact of adrenergic stress on cancer cells, immunosuppression, and immunotherapeutic response. *Cancer Immunol. Immunother.* 63, 1115–1128 (2014).
- [130] Hamamoto, A. et al. Modulation of primary cilia length by melanin-concentrating hormone receptor 1. *Cell Signal.* 28, 572–584 (2016).
- [131] Shiwaku, H., Umino, A., Umino, M. & Nishikawa, T. Phencyclidine-induced dysregulation of primary cilia in the rodent brain. *Brain Res.* 1674, 62–69 (2017).

- [132] Miyoshi, K. et al. Lack of dopaminergic inputs elongates the primary cilia of striatal neurons. *PLoS ONE* 9, e97918 (2014).
- [133] Avasthi, P. et al. A chemical screen identifies class a g-protein coupled receptors as regulators of cilia. *ACS Chem. Biol.* 7, 911-919 (2012).
- [134] Boisvieux-Ulrich, E., Laine, M. C. & Sandoz, D. In vitro effects of benzodiazepines on ciliogenesis in the quail oviduct. *Cell. Motil. Cytoskeleton* 8, 333-344 (1987).
- [135] Kieran, M. W. et al. Phase I study of oral sonidegib (LDE225) in pediatric brain and solid tumors and a phase II study in children and adults with relapsed medulloblastoma. *Neuro Oncol.* 19, 1542-1552 (2017).
- [136] Olive, K. P. et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 324, 1457-1461 (2009).
- [137] Sekulic, A. et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N. Engl. J. Med.* 366, 2171-2179 (2012).
- [138] Rimkus, T. K., Carpenter, R. L., Qasem, S., Chan, M. & Lo, H. W. Targeting the Sonic Hedgehog signaling pathway: review of Smoothened and GLI inhibitors. *Cancers* 8, 22 (2016).
- [139] Kool, M. et al. Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. *Cancer Cell* 25, 393-405 (2014).
- [140] Zhao, X. et al. A transposon screen identifies loss of primary cilia as a mechanism of resistance to SMO inhibitors. *Cancer Discov.* 7, 1436-1449 (2017).
- [141] Catenacci, D. V. et al. Randomized phase Ib/II study of gemcitabine plus placebo or vismodegib, a Hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer. *J. Clin. Oncol.* 33, 4284-4292 (2015).
- [142] Nolan-Stevaux, O. et al. GLI1 is regulated through Smoothened-independent mechanisms in neoplastic pancreatic ducts and mediates PDAC cell survival and transformation. *Genes Dev.* 23, 24-36 (2009).
- [143] Rhim, A. D. et al. Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma. *Cancer Cell* 25, 735-747 (2014).
- [144] Ozdemir, B. C. et al. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. *Cancer Cell* 25, 719-734 (2014).
- [145] Stathis, A. et al. Phase I trial of the oral smoothened inhibitor sonidegib in combination with paclitaxel in patients with advanced solid tumors. *Invest. New Drugs* 35, 766-772 (2017).
- [146] Di Mauro, C. et al. Hedgehog signalling pathway orchestrates angiogenesis in triple-negative breast cancers. *Br. J. Cancer* 116, 1425-1435 (2017).
- [147] Larsen, A. R. et al. Repurposing the antihelminthic mebendazole as a hedgehog inhibitor. *Mol. Cancer Ther.* 14, 3-13 (2015).
- [148] De Witt, M. et al. Repurposing mebendazole as a replacement for vincristine for the treatment of brain tumors. *Mol. Med.* 23, 50-56 (2017).
- [149] Wang, J. & Barr, M. M. Ciliary extracellular vesicles: txt msg organelles. *Cell. Mol. Neurobiol.* 36, 449-457 (2016).
- [150] Nager, A. R. et al. An actin network dispatches ciliary GPCRs into extracellular vesicles to modulate signaling. *Cell* 168, 252-263.e14 (2017).
- [151] Fooksman, D. R. et al. Functional anatomy of T cell activation and synapse formation. *Annu. Rev. Immunol.* 28, 79-105 (2010).
- [152] Prosser, S. L. & Morrison, C. G. Centrin2 regulates CP110 removal in primary cilium formation. *J. Cell Biol.* 208, 693-701 (2015).
- [153] Finetti, F. et al. Intraflagellar transport is required for polarized recycling of the TCR/CD3 complex to the immune synapse. *Nat. Cell Biol.* 11, 1332-1339 (2009).
- [154] Lau, C. I., Barbarulo, A., Solanki, A., Saldana, J. I. & Crompton, T. The kinesin motor protein Kif7 is required for T cell development and normal MHC expression on thymic epithelial cells (TEC) in the thymus. *Oncotarget* 8, 24163-24176 (2017).
- [155] Mukhopadhyay, S. et al. TULP3 bridges the IFT-A complex and membrane phosphoinositides to promote trafficking of G protein-coupled receptors into primary cilia. *Genes Dev.* 24, 2180-2193 (2010).
- [156] Noda, K., Kitami, M., Kitami, K., Kaku, M. & Komatsu, Y. Canonical and noncanonical intraflagellar transport regulates craniofacial skeletal development. *Proc. Natl Acad. Sci. USA* 113, E2589-E2597 (2016).
- [157] Outeda, P. et al. Polycystin signaling is required for directed endothelial cell migration and lymphatic development. *Cell Rep.* 7, 634-644 (2014).
- [158] Lee, J. E. & Gleeson, J. G. A systems-biology approach to understanding the ciliopathy disorders. *Genome Med.* 3, 59 (2011).
- [159] Yuan, S. & Sun, Z. Expanding horizons: ciliary proteins reach beyond cilia. *Annu. Rev. Genet.* 47, 353-376 (2013).

- [160] Wheway, G. et al. An siRNA-based functional genomics screen for the identification of regulators of ciliogenesis and ciliopathy genes. *Nat. Cell Biol.* 17, 1074–1087 (2015).
- [161] Brooks, E. R. & Wallingford, J. B. Multiciliated cells. *Curr. Biol.* 24, R973–982 (2014).
- [162] Yaghi, A. & Dolovich, M. B. Airway epithelial cell cilia and obstructive lung disease. *Cells* 5, 40 (2016).
- [163] Tilley, A. E., Walters, M. S., Shaykhiev, R. & Crystal, R. G. Cilia dysfunction in lung disease. *Annu. Rev. Physiol.* 77, 379–406 (2015).
- [164] Horani, A., Ferkol, T. W., Dutcher, S. K. & Brody, S. L. Genetics and biology of primary ciliary dyskinesia. *Paediatr. Respir. Rev.* 18, 18–24 (2016).
- [165] Jensen, V. L. et al. Formation of the transition zone by Mks5/Rpgrip1L establishes a ciliary zone of exclusion (CIZE) that compartmentalises ciliary signalling proteins and controls PIP2 ciliary abundance. *EMBO J.* 34, 2537–2556 (2015).
- [166] Spektor, A., Tsang, W. Y., Khoo, D. & Dynlacht, B. D. Cep97 and CP110 suppress a cilia assembly program. *Cell* 130, 678–690 (2007).
- [167] Xu, Q. et al. Phosphatidylinositol phosphate kinase PIPK $\gamma$  and phosphatase INPP5E coordinate initiation of ciliogenesis. *Nat. Commun.* 7, 10777 (2016).
- [168] Mojarad, B. A. et al. CEP19 cooperates with FOP and CEP350 to drive early steps in the ciliogenesis programme. *Open Biol.* 7, 170114 (2017).
- [169] Kanie, T. et al. The CEP19-RABL2 GTPase complex binds IFT-B to initiate intraflagellar transport at the ciliary base. *Dev. Cell* 42, 22–36.e12 (2017).
- [170] Plotnikova, O. V. et al. Calmodulin activation of Aurora-A kinase (AURKA) is required during ciliary disassembly and in mitosis. *Mol. Biol. Cell* 23, 2658–2670 (2012).
- [171] Riparbelli, M. G., Cabrera, O. A., Callaini, G. & Megraw, T. L. Unique properties of *Drosophila* spermatocyte primary cilia. *Biol. Open* 2, 1137–1147 (2013).
- [172] Shinohara, K. et al. Absence of radial spokes in mouse node cilia is required for rotational movement but confers ultrastructural instability as a trade-off. *Dev. Cell* 35, 236–246 (2015).
- [173] Jensen, C. G., Davison, E. A., Bowser, S. S. & Rieder, C. L. Primary cilia cycle in PtK1 cells: effects of colcemid and taxol on cilia formation and resorption. *Cell. Motil. Cytoskeleton* 7, 187–197 (1987).
- [174] Kavoi, B. M., Makanya, A. N. & Kiama, S. G. Anticancer drug vinblastine sulphate induces transient morphological changes on the olfactory mucosa of the rabbit. *Anat. Histol. Embryol.* 41, 374–387 (2012).
- [175] Wang, S., Wei, Q., Dong, G. & Dong, Z. ERK-mediated suppression of cilia in cisplatin-induced tubular cell apoptosis and acute kidney injury. *Biochim. Biophys. Acta* 1832, 1582–1590 (2013).
- [176] Huang, J. et al. Trichostatin A reduces cisplatin-induced ototoxicity through the STAT6 signaling pathway. *Int. J. Mol. Med.* 36, 493–500 (2015).
- [177] Mount, R. J., Takeno, S., Wake, M. & Harrison, R. V. Carboplatin ototoxicity in the chinchilla: lesions of the vestibular sensory epithelium. *Acta Otolaryngol. Suppl.* 519, 60–65 (1995).
- [178] Kim, J. et al. Itraconazole, a commonly used antifungal that inhibits Hedgehog pathway activity and cancer growth. *Cancer Cell* 17, 388–399 (2010).
- [179] Valencia-Gattas, M., Conner, G. E. & Fregien, N. L. Gefitinib, an EGFR tyrosine kinase inhibitor, prevents smoke-mediated ciliated airway epithelial cell loss and promotes their recovery. *PLoS ONE* 11, e0160216 (2016).
- [180] Takahashi, K., Nagai, T., Chiba, S., Nakayama, K. & Mizuno, K. Glucose deprivation induces primary cilium formation through mTORC1 inactivation. *J. Cell Sci.* 10.1242/jcs.208769 (2018).
- [181] Wang, H. et al. Hsp90 $\alpha$  forms a stable complex at the cilium neck for the interaction of signalling molecules in IGF-1 receptor signalling. *J. Cell Sci.* 128, 100–108 (2015).